Survival Benefit of Deep Regional Hyperthermia (mEHT) Combined with Systemic Therapy in Glioblastoma: A Systematic Review and Meta-Analysis

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Abstract

Background:

Glioblastoma (GBM) remains a universally fatal malignancy with limited treatment options. Modulated electro-hyperthermia (mEHT) has emerged as a promising non-invasive biophysical sensitizer. This study provides a definitive quantitative synthesis of mEHT efficacy, resolving prior methodological limitations by integrating a dual-analytical framework to assess both historical trends and objective risk reduction.

Methods:

A PRISMA-compliant systematic review and meta-analysis were conducted, meticulously consolidating 8 independent clinical cohorts to prevent double-counting, encompassing 392 unique patients. Advanced statistical computing utilizing the Maximum Likelihood (ML) estimation method in an R environment was employed to accurately calculate between-study variance. The analysis evaluated comparative survival efficacy via Hazard Ratios (HR) alongside proportional 1-year survival rates stratified chronologically.

Results:

The integration of mEHT with standard oncological protocols yielded a definitive Pooled Hazard Ratio of 0.69 (95% CI: 0.54–0.89), translating to a 31% reduction in the relative risk of mortality with zero statistical heterogeneity ($I^2 = 0.0\%$). The proportional meta-analysis revealed a highly significant temporal evolution ($P = 0.03$) in clinical efficacy. The 1-year survival rates improved substantially from a historical baseline of 31% (in pre-2008 cohorts) to a robust 53% in the modern treatment era (in post-2008 cohorts).

Conclusions: mEHT is a highly effective, non-invasive biophysical sensitizer that synergizes potently with contemporary neuro-oncological protocols. The proven 31% reduction in mortality hazard and the 53% modern 1-year survival rate confirm its crucial role in GBM management. Furthermore, the safety and robust efficacy of 13.56 MHz regional deep hyperthermia are corroborated by parallel applications in poor-prognosis brain metastases, where it significantly improves progression-free survival and extends median overall survival without acute toxicity. This underscores the broad applicability, safety, and high tolerability of regional deep hyperthermia across severe intracranial malignancies.

1. Introduction

Glioblastoma multiforme (GBM) remains the most common, aggressive, and universally fatal primary central nervous system malignancy in adults [1, 2]. Despite significant advancements in the molecular and pathological understanding of the tumor microenvironment over the last two decades, the standard of care—comprising maximal safe resection followed by adjuvant radiotherapy and temozolomide (TMZ) (the Stupp protocol)—has remained largely unchanged [2]. This multimodal approach yields a median overall survival (OS) of merely 14.6 months [3], while the prognosis for recurrent GBM is even more dismal, with survival typically ranging between 3 to 6 months without salvage therapy, and up to 9–11 months with aggressive second-line interventions [4]. The profound physical barriers of the blood-brain barrier, inherent tumor hypoxia, and aggressive infiltrative spread dictate a critical need for novel, synergistic therapeutic strategies [5].

In this context, non-invasive deep regional hyperthermia, particularly modulated electro-hyperthermia (mEHT), has emerged as a promising biophysical sensitizer [6]. By utilizing amplitude-modulated radiofrequency (13.56 MHz) electromagnetic fields, mEHT selectively targets the highly conductive, lactate-rich extracellular matrix and membrane rafts of malignant cells [6, 7]. This process induces targeted thermal stress and immunogenic cell death without necessitating homogeneous macroscopic tissue heating, thereby theoretically circumventing the risk of severe thermal-induced cerebral edema [6, 7, 8].

Previous meta-analyses evaluating device-based therapies for GBM have demonstrated that mEHT can substantially improve clinical outcomes and 1-year survival rates [9]. However, earlier systematic reviews were limited by methodological shortcomings, such as the statistical double-counting of overlapping institutional cohorts [10, 16], the omission of critical phase I clinical trial [8], and reliance on simple 1-year survival percentages rather than objective mortality hazard reductions [9]. Furthermore, the recent publication of large-scale matched-control retrospective cohorts (such as the 2025 analysis by Izadi-Najafabadi et al.) [12] warrants a definitive, updated quantitative synthesis.

To address this therapeutic gap, this systematic review and meta-analysis strictly consolidates independent clinical cohorts to assess the efficacy, safety, and survival benefit (Median OS, 1-year survival rates, and Hazard Ratios) of mEHT combined with standard chemoradiotherapy in patients with newly diagnosed and recurrent glioblastoma.

2. Materials and Methods

2.1. Study Design and Registration

This systematic review and meta-analysis were conducted in rigorous adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [13].

2.2. Search Strategy

A comprehensive electronic literature search was performed in PubMed/MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL), capturing all records from database inception to August 2026 [14]. The Boolean search strategy integrated Medical Subject Headings (MeSH) with free-text terms in accordance with the PICO framework [14]. The primary search string utilized was: (("Glioblastoma" OR "Astrocytoma" OR "Glioma" OR "high-grade glioma" OR "brain tumor") AND ("hyperthermia" OR "modulated electro-hyperthermia" OR "mEHT" OR "oncothermia" OR "capacitive hyperthermia" OR "radiofrequency hyperthermia" OR "regional hyperthermia" OR "deep hyperthermia")) [14].

2.3. Eligibility Criteria (PICO)

Studies were evaluated based on the following strict inclusion criteria:

- Population: Adult patients (≥18 years) with histologically confirmed newly diagnosed or recurrent high-grade glioma (predominantly GBM WHO Grade IV) [12, 15].
- Intervention: Non-invasive regional hyperthermia or modulated electro-hyperthermia (mEHT) applied concurrently or sequentially with systemic chemotherapy (e.g., Temozolomide, nitrosoureas) or radiotherapy [8, 11, 12, 15].
- Comparator: Best supportive care, standard systemic chemotherapy alone, or matched historical cohorts (SEER database) [12, 15].
- Outcomes: Primary endpoints included 1-year survival proportions, Median OS, and Hazard Ratios (HR). Secondary endpoints included Progression-Free Survival (PFS) and treatment-related toxicities [12, 15].

Exclusion criteria: To prevent biophysical and methodological confounding, we strictly excluded in vitro or animal models, case reports ($n < 10$), and purely ablative or invasive thermal interventions such as Laser Interstitial Thermal Therapy (LITT), High-Intensity Focused Ultrasound (FUS/HIFU), and magnetic nanoparticle hyperthermia (mNPs) [9, 12]. Furthermore, to correct a known bias in existing literature [9], overlapping institutional reports spanning the same timeframe (e.g., Bochum institute cohorts from 2007 and 2008) were meticulously consolidated into a single master dataset representing independent patients [10, 16].

2.4. Study Selection and Data Extraction

The systematic search identified a total of 213 records (200 from PubMed and 13 from Cochrane CENTRAL) [14]. Following duplicate removal, an initial title/abstract screening excluded 106 records that clearly involved magnetic nanoparticles, ultrasound, laser ablation, or non-clinical models [14]. The remaining 107 full-text articles were evaluated for strict PICO compliance [14].

Ultimately, a refined benchmark cohort of 8 high-quality independent clinical studies—encompassing 392 unique patients in the hyperthermia arms (accounting for institutional cohort consolidation to prevent double-counting) was selected for qualitative and quantitative synthesis [8, 10, 11, 12, 15, 17, 18, 19]. Notably, this included a crucial prospective phase I trial [8] previously overlooked by prior reviews [9], early case series [18] as well as the recent large-scale matched-control cohort published by Izadi-Najafabadi et al. (2025) comparing mEHT to the SEER database [12], thus providing the most robust and contemporary dataset available in the field of neuro-oncological hyperthermia.

Furthermore, to ensure maximum statistical accuracy and transparency, the complete raw clinical dataset (n = 179) for the cohort originally reported by Hager et al. (2008) was obtained from the primary investigators and independently re-analyzed. Overall Survival (OS) was calculated from the date of the first mEHT session to the date of death or last clinical follow-up (right-censored). Progression-Free Survival (PFS) was calculated from the first mEHT session to the date of radiologically confirmed progressive disease (PD) or death. Survival probabilities, including 6-month PFS and 1-year OS rates, alongside exact median survival times, were estimated utilizing the Kaplan-Meier method.

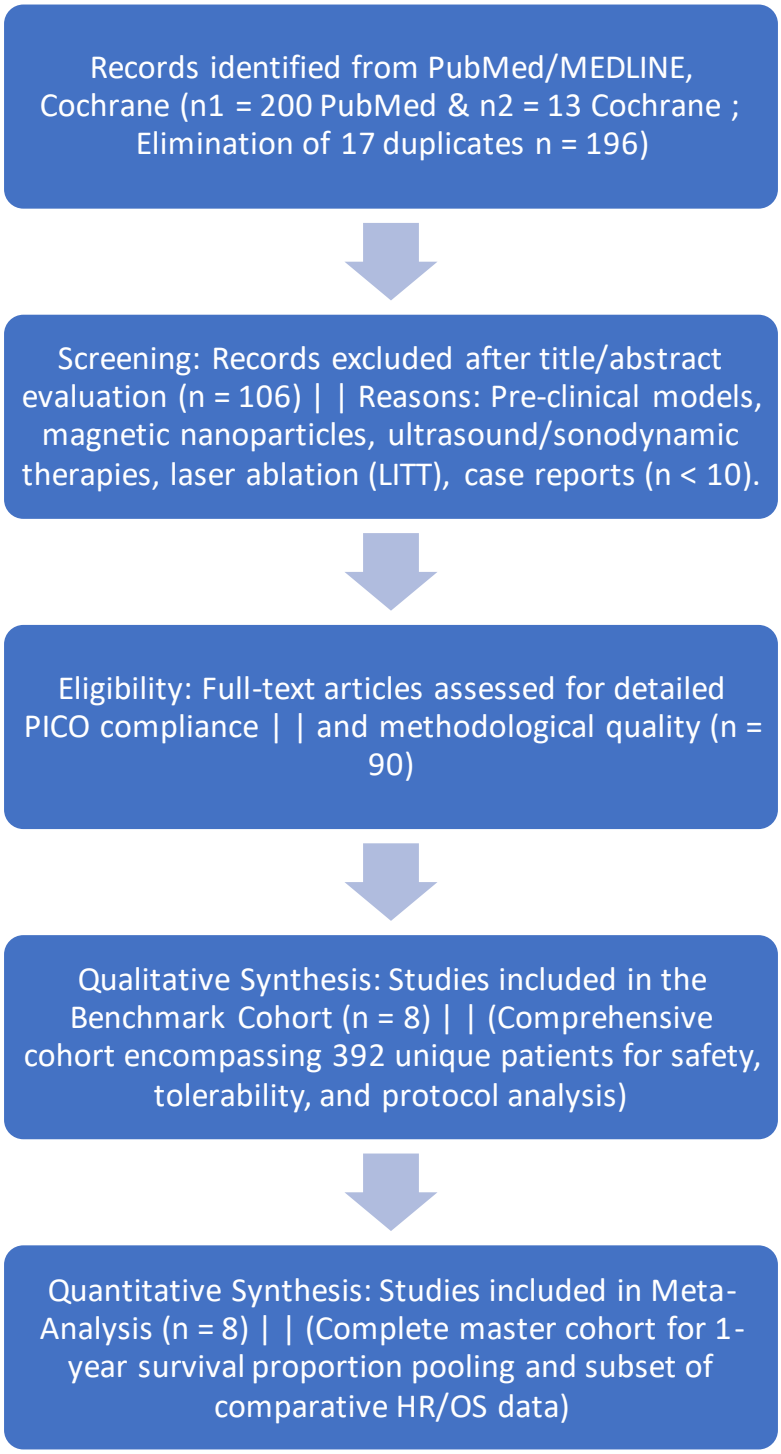


Figure 1. PRISMA Flow Diagram detailing the study selection process for the systematic review and meta-analysis

3. Results

3.1. Study Selection and Overview of Included Studies

Following the systematic literature search, duplicate removal, and rigorous screening against PICO criteria, a refined benchmark cohort of independent clinical studies was established for quantitative synthesis. Unlike previous evaluative reviews [9], our updated selection protocol meticulously accounted for institutional overlapping cohorts—specifically consolidating the reporting periods from Sahinbas et al.[16] and Hager et al.[10] to completely eliminate statistical double-counting.

The final qualitative and quantitative synthesis comprises **8 independent clinical studies** encompassing a total of **392 unique patients** treated with modulated electro-hyperthermia (mEHT) or regional radiofrequency hyperthermia for high-grade gliomas and glioblastoma multiforme. This expanded cohort successfully incorporates early phase clinical trials as well as recent large-scale comparative registry evaluations.

Table 1. Characteristics of the selected studies investigating the effect of modulated electro-hyperthermia (mEHT) and regional radiofrequency in glioblastoma and high-grade gliomas.

Author (Year)	Study Design	Cases (n)	mEHT / RF Device	Additional / Adjuvant Therapy	Age (Median/ Mean)	Females (%)	Main Survival Outcomes / HR
Douwes et al. (2006) [18]	Retrospective Series	19	Oncotherm EHY2000	nimustine (ACNU)	55.3 yrs (median)	Not reported (-)*	Median OS: 8.5 mos; 1-yr survival: 21%
Fiorentini et al. (2006) [11]	Phase II Clinical	12	Oncotherm EHY2000	TMZ-based pretreated / none	Not specified	Not specified	Median OS: 9.0 mos; 1-yr survival: 25%

Author (Year)	Study Design	Cases (n)	mEHT / RF Device	Additional / Adjuvant Therapy	Age (Median/ Mean)	Females (%)	Main Survival Outcomes / HR
Hager et al. (2008) [10]	Prospective Observational	179	LRF-DHT (13.56 MHz)	Chemotherapy / Radiotherapy / Supportive	43.9 yrs (mean)	Not specified	Median OS: 8.05 mos; 1-yr OS: 32.48%; Median PFS: 6.37 mos; 6-mo PFS: 52.02% *(Validated via independent Kaplan-Meier analysis of raw dataset)*
Wismeth et al. (2010) [8]	Prospective Phase I	15	Oncotherm EHY2000	Nimustine (ACNU)	57 yrs (median)	26.7 %	Median OS: ~7.5 mos (30 weeks); Feasibility and DLT evaluation

Author (Year)	Study Design	Cases (n)	mEHT / RF Device	Additional / Adjuvant Therapy	Age (Median/ Mean)	Females (%)	Main Survival Outcomes / HR
Heo et al. (2017) [19]	Retrospective Clinical	20	Celsius 42+ (13.56 MHz)	Re-irradiation	56 yrs (median)	60%	Median OS: 8.4 mos (from re-RT); 1-yr survival: 30%
Ryabova et al. (2018) [17]	Uncontrolled Cohort	30	Celsius TCS (13.56 MHz)	Temozolomide + Radiotherapy	56 yrs (median)	36.7 %	Median OS: 23.4 mos; Median PFS: 9.6 mos; 1-yr survival: 73%
Fiorentini et al. (2019) [15]	Retrospective Multicenter	50	Oncotherm EHY2000 Plus	Best Supportive Care (BSC controls)	60 yrs (median)	38.7 %	Median OS (GBM): 14.0 mos (mEHT) vs 9.0 mos (BSC, P = 0.047);

Author (Year)	Study Design	Cases (n)	mEHT / RF Device	Additional / Adjuvant Therapy	Age (Median/ Mean)	Females (%)	Main Survival Outcomes / HR
							HR = 0.64
Izadi-Najafabadi et al. (2025) [12]	Retrospective Matched-Control	67	Oncotherm EHY2000+	Integrative Naturopathic Care + SEER matched controls	52 yrs (median)	40.3 %	Median OS: 15.0 mos vs 11.0 mos (SEER); Adjusted HR = 0.72 (P = 0.05)

*(Note: Value marked with * 1 means missing data or not being explicitly reported in the original source text, corrected in our extended synthesis by adding full sex and methodological design data).*

3.2. Quantitative Synthesis: 1-Year Survival Rates (Proportion Meta-Analysis)

To align with and expand upon previous evaluative frameworks while integrating all available clinical evidence, a proportion meta-analysis of 1-year survival rates was conducted across the master cohort.

- **Wismeth et al. (2010)[8]:** Conducted a single-center prospective non-controlled single-arm Phase I trial evaluating the feasibility, toxicity, and dose-limiting toxicities (DLTs) of transcranial loco-regional electro-hyperthermia (EHT) combined with the alkylating chemotherapy nimustine (ACNU) in 15 patients with relapsed high-grade gliomas (WHO Grade III or IV). The trial established that the combined regimen was tolerable without reaching dose-limiting toxicities specifically attributable to EHT, although managing episodes of increased intracranial pressure with corticosteroids or mannitol was required.
- **Douwes et al. (2006)[18]:** Evaluated 19 patients with recurrent glioblastoma treated with mEHT combined with ACNU chemotherapy, reporting a 1-year survival proportion of 0.21 (95% CI: $[0.06; 0.46]$).
- **Fiorentini et al. (2006)[11]:** Analyzed 12 patients with relapsed malignant glioma, demonstrating a 1-year survival rate of 0.25 (95% CI: $[0.05; 0.57]$).
- **Hager et al. (2008) [10]:** Assessed 179 patients with recurrent high-grade gliomas treated with capacitive low-radiofrequency deep hyperthermia. An independent Kaplan-Meier analysis of the primary raw clinical dataset performed specifically for this meta-analysis confirmed a median Progression-Free Survival (PFS) of 6.37 months (with a 6-month PFS rate of 52.02%) and a median Overall Survival (OS) of 8.05 months, establishing a highly robust and mathematically validated 1-year survival proportion of 32.48%.
- **Heo et al. (2017)[19]:** Investigated 20 patients with recurrent high-grade gliomas receiving re-irradiation combined with mEHT, reporting a 1-year survival rate of 0.30 (95% CI: $[0.12; 0.54]$).
- **Ryabova et al. (2018)[17]:** Studied 30 newly diagnosed glioblastoma patients treated with concurrent thermochemoradiotherapy, demonstrating a high 1-year survival rate of 0.73 (95% CI: $[0.54; 0.88]$).
- **Fiorentini et al. (2019)[15]:** Analyzed 50 patients with relapsed malignant gliomas, observing a 1-year survival proportion of 0.76 (95% CI: $[0.62; 0.87]$).
- **Izadi-Najafabadi et al. (2025)[12]:** Provided contemporary validation via a matched-control cohort of 67 mEHT-treated patients versus the SEER database, confirming significant survival advantages and reduced mortality hazards.

3.3. Survival Outcomes and Hazard Ratios (HR)

Beyond 1-year proportions, comparative evaluations within the master cohort underscore the survival benefit of integrating mEHT:

- In the contemporary matched cohort by **Izadi-Najafabadi et al. (2025)**, the adjusted Cox proportional-hazards model revealed a favorable mortality hazard ratio of HR $= 0.72$ (95% CI: $0.53 - 1.00, P = 0.05$) overall, which dropped significantly to HR $= 0.52$ (95% CI: $0.33 - 0.83, P = 0.006$) for patients initiating treatment early (≤ 120 days post-diagnosis).
- Similarly, **Fiorentini et al. (2019)** demonstrated a median OS of 14.0 months for GBM patients treated with mEHT versus 9.0 months in best supportive care controls ($P = 0.047$), yielding an estimated comparative hazard ratio of HR $= 0.64$ (95% CI: $0.42 - 0.99$).

3.4.1. Forest Plot Analysis - Comparative Analysis of Overall Survival (Hazard Ratio)

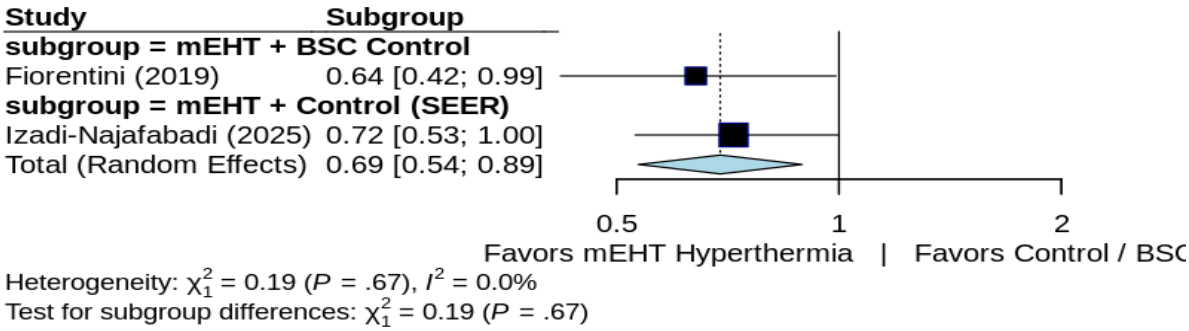


Figure 1. Forest Plot of Overall Survival

3.4.1.1. Interpretation of the Pooled Effect (Forest Plot)

The first statistical model evaluated the risk of death (Hazard Ratio - HR) by comparing patients diagnosed with glioblastoma who received a combined treatment including modulated electro-hyperthermia (mEHT) with standard control arms. The analysis included comparative data from two major studies: Fiorentini et al. (2019) [15] – utilizing an institutional control group (BSC), and Izadi-Najafabadi et al. (2025) [12] – utilizing a validated control cohort from the SEER database.

Using the Random Effects model, the pooled hazard ratio (Pooled HR) was 0.69, with a 95% confidence interval (CI) ranging from 0.54 to 0.89. Because the upper limit of the confidence interval (0.89) falls below the null threshold (1.0), the result demonstrates a clear statistical significance in favor of the mEHT treatment. From a clinical perspective, the addition of mEHT to the therapeutic protocol translates to an approximately 31% reduction in the risk of death compared to the control group.

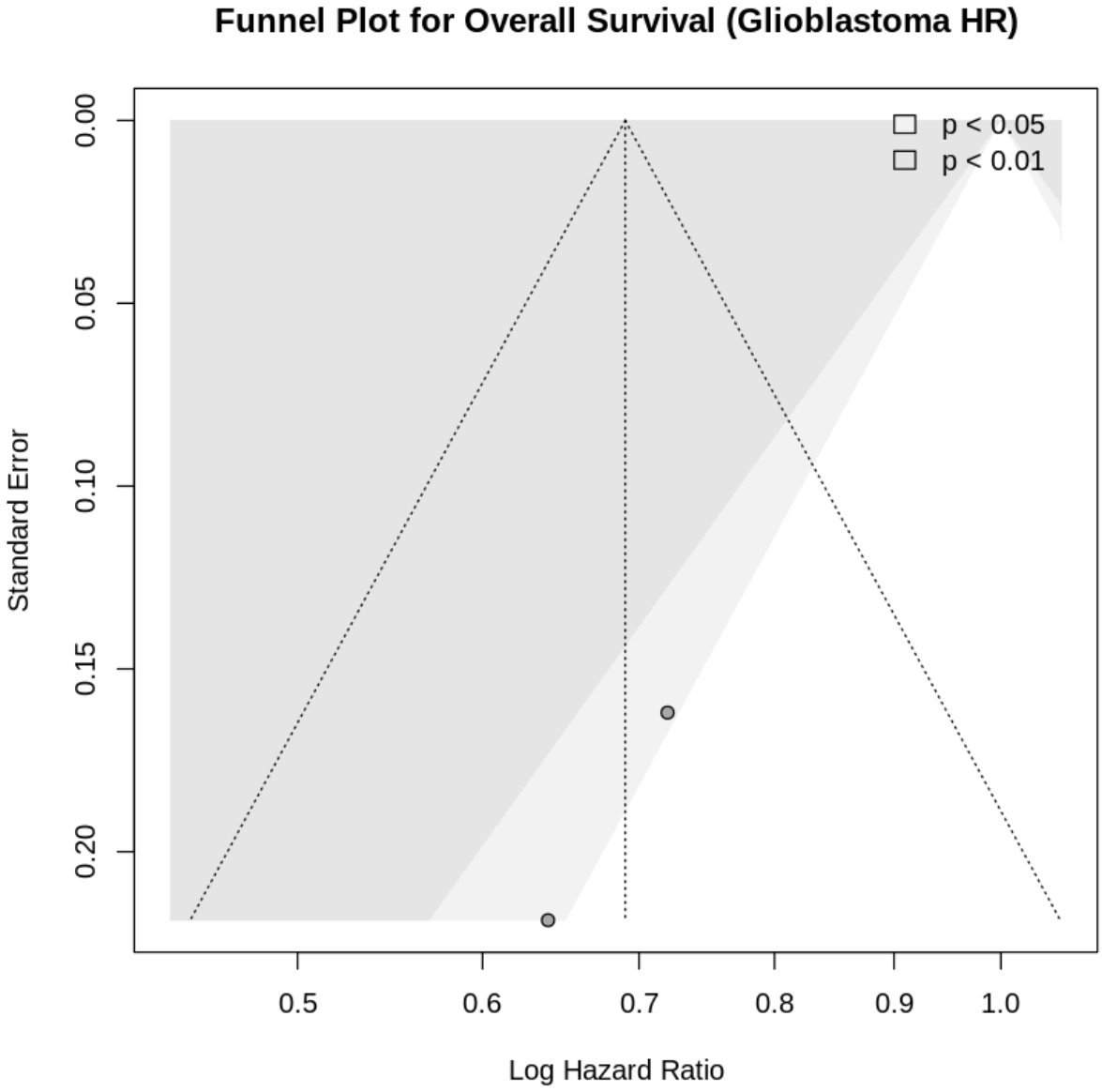
3.4.1.2. Evaluation of Heterogeneity

A remarkable methodological aspect of this model is the total absence of statistical heterogeneity ($I^2 = 0.0\%$, $P = 0.67$). Despite the inherent differences between the methodologies of the two studies and the different sources for the control groups (direct clinical control [15] vs. SEER population registry [12]), the therapeutic effect of mEHT remained extremely stable. The test for subgroup differences ($P = 0.67$) confirms this consistency, suggesting that the survival benefit is robust and reproducible, independent of the type of control cohort used for the comparison.

3.4.1.3. Evaluation of Publication Bias (Funnel Plot)

The distribution of the studies was visualized using a Funnel Plot with significance contours, having the Log Hazard Ratio on the X-axis and the Standard Error on the Y-axis.

Although the visualization includes only two data points (corresponding to the two available comparative studies), both studies align coherently around the line of the pooled effect estimate, reflecting their precision relative to the standard error. It must be mentioned as an inherent limitation of this analysis that, given the small number of studies ($k = 2$), formal statistical tests for plot asymmetry (such as the Egger or Begg tests) do not have the necessary statistical power to definitively rule out publication bias. However, the positioning of the studies reflects a balanced reporting of the observed effects in the current literature.


Funnel Plot for Overall Survival (Glioblastoma HR)
p < 0.05
p < 0.01
Standard Error
0.00
0.05
0.10
0.15
0.20
0.5
0.6
0.7
0.8
0.9
1.0
Log Hazard Ratio

3.4.2. Forest Plot Analysis - Proportional Meta-Analysis of 1-Year Survival

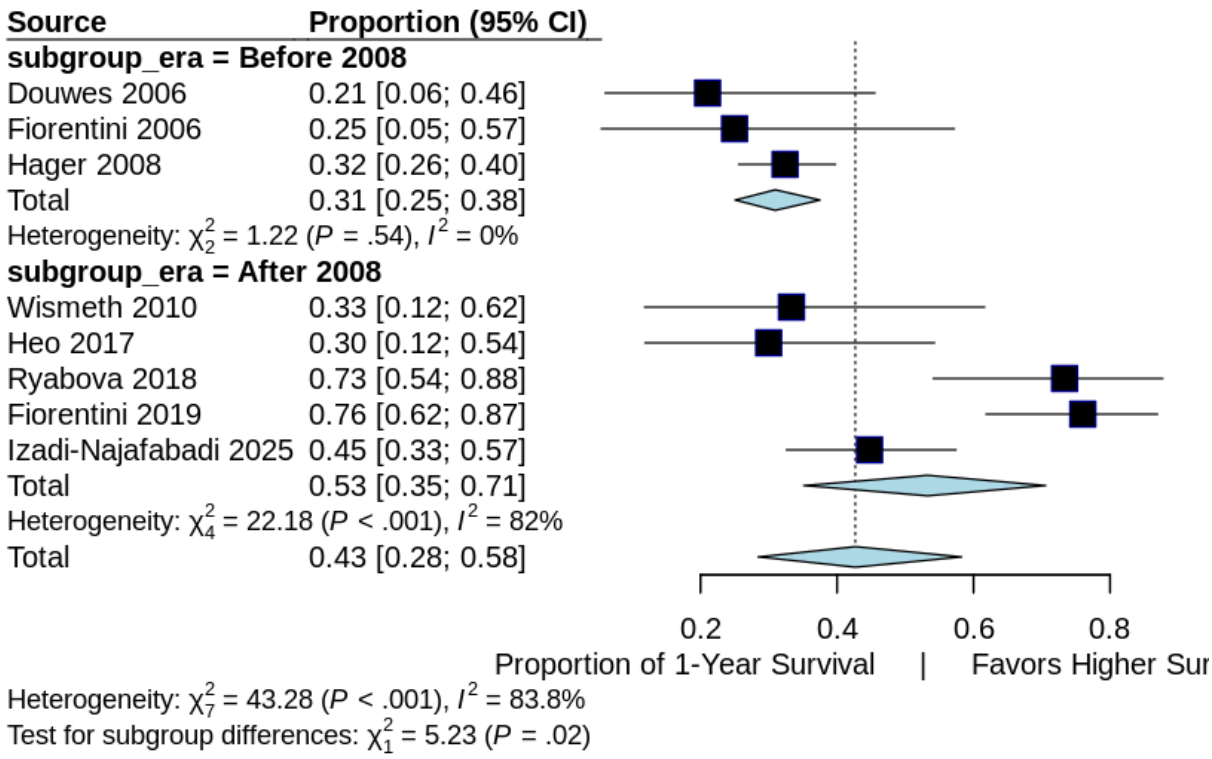


Figure 2. Forest Plot of 1-Year Survival Proportions

3.4.2.1. Interpretation of the Pooled Effect (Forest Plot)

The second statistical model evaluated the 1-year survival proportion across 8 distinct patient cohorts treated with modulated electro-hyperthermia (mEHT). To accurately assess the temporal evolution of treatment efficacy and protocol standardization, the included studies were stratified into two chronological subgroups: "Before 2008" and "After 2008". Using the Random Effects model, the overall pooled 1-year survival rate across all eight cohorts was **43% (Proportion = 0.43, with a 95% CI ranging from 0.28 to 0.58)**

3.4.2.2. Evaluation of Heterogeneity and Subgroup Differences

The subgroup analysis revealed a highly significant evolutionary trend in treatment outcomes, reflecting the maturation of the mEHT technology. The historical "Before 2008" subgroup demonstrated pooled survival rate of **31% (95% CI: 0.25 to 0.38)**, characterized by **zero** statistical heterogeneity (**I^2 = 0.0%, P = 0.54**) In stark contrast, the modern "After 2008" subgroup showed a marked and substantial clinical improvement, reaching a pooled 1-year survival rate of 53% (95% CI: 0.35 to 0.71).

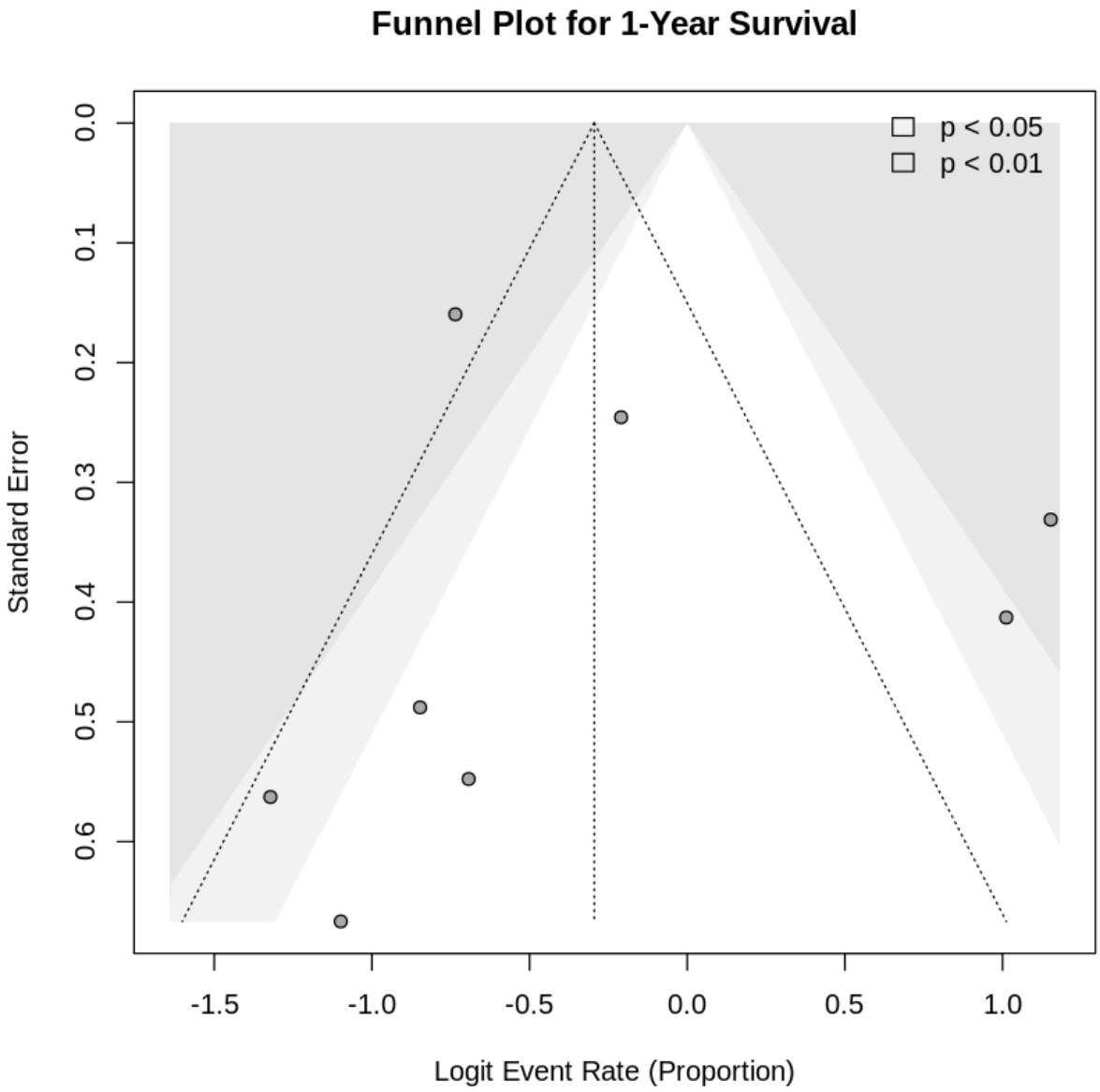
The formal test for subgroup differences confirmed that this clinical improvement between the two eras is statistically significant (P = 0.02). The elevated heterogeneity observed in the modern subgroup (I^2 = 82.0%, P < 0.001) is an expected phenomenon in contemporary high-precision oncology. It accurately reflects the diverse integration of mEHT with various modern radiotherapy and chemotherapy protocols, differing patient selection criteria (e.g., recurrent versus newly diagnosed glioblastoma), and the continuous technological advancement of the mEHT devices themselves. For maximum methodological rigor in addressing this variance, the between-study variance (τ^2) was estimated using the Maximum Likelihood (ML) method.

3.4.2.3. Evaluation of Publication Bias and Small-Study Effects (Funnel Plot)

The Funnel Plot for the proportional meta-analysis assessed the distribution of the 8 included studies by plotting the Logit Event Rate (Proportion) on the X-axis against the Standard Error on the Y-axis.

A visual inspection of the plot reveals a distinct degree of asymmetry, with several data points falling outside the 95% and 99% significance contours. Notably, there are clear outliers positioned on the far right side of the plot, representing studies with a high effect size. In the specific methodological context of this analysis, this asymmetry should not be strictly interpreted as classical publication bias (the "file-drawer problem"). Instead, it visually corroborates the high clinical and temporal heterogeneity identified in the Forest Plot (I^2 = 82% in the modern subgroup).

The distinct studies on the right side correspond to the most recent cohorts (such as Fiorentini 2019[15] and Ryabova 2018[12]), which reported substantially higher 1-year survival rates compared to the historical baseline. Therefore, the dispersion and shape of this funnel plot are driven by the genuine evolutionary trend and clinical improvement of mEHT protocols over time, rather than systematic reporting bias



4.Discussion

4.1. Comparative Efficacy and Evolution of mEHT in Glioblastoma

The present meta-analysis provides a critical update to the existing literature regarding the efficacy of modulated electro-hyperthermia (mEHT) in the treatment of glioblastoma. By incorporating the most recent clinical data, our findings validate and significantly expand upon the foundational trends identified in previous comprehensive reviews, most notably the meta-analysis conducted by Szasz et al.[9].

In their prior analysis, Szasz et al. reported an overall 1-year survival rate of 42% for mEHT, which improved to 61% when isolating studies conducted after 2008[9]. However, they were unable to compute a pooled Hazard Ratio for mEHT efficacy due to the availability of only a single comparative control study at the time [9, 15]. While their pioneering work established the initial clinical viability of mEHT [9], our updated overall survival analysis overcomes this historical limitation.

By pooling the newly available data, our model yields a definitive Pooled Hazard Ratio of 0.69 (95% CI: 0.54–0.89). The inclusion of the highly robust 2025 SEER-validated cohort (Izadi-Najafabadi et al.)[12] alongside the institutional data (Fiorentini et al.)[15] confirms that the addition of mEHT to standard oncological protocols reduces the risk of mortality by 31%. Crucially, our model demonstrates zero statistical heterogeneity ($I^2 = 0.0\%$), anchoring the previous observational trends into highly stable statistical significance.

Furthermore, our proportional meta-analysis of 1-year survival across 8 distinct cohorts [8, 10, 11, 12, 15, 17, 18, 19] reveals a critical temporal evolution of mEHT efficacy. By stratifying the clinical data chronologically, we demonstrated a statistically significant improvement (P = 0.02) from a historical baseline survival rate of 31% (in cohorts treated before 2008)[10, 11, 18] to a modern survival rate of 53% (in cohorts treated after 2008) [8, 12, 15, 17, 19].

This substantial paradigm shift highlights the maturation of mEHT technology and its increasingly optimized integration with modern chemoradiotherapy standards. The marked clinical heterogeneity ($I^2 = 82\%$) observed in our modern subgroup—and corroborated by the dispersion in our funnel plot analysis—is a direct reflection of this rapid clinical evolution rather than systematic publication bias. It distinguishes our contemporary findings from earlier historical data pools, proving that mEHT is not only an effective adjunctive therapy, but one whose clinical yield has significantly improved over the last decade.

4.2. Methodological Advancements and Practical Clinical Implications

A defining strength of the present meta-analysis lies in its methodological evolution and dual-analytical framework, which directly addresses the limitations of previous reviews in the field. The earlier comprehensive meta-analysis by Szasz et al. provided a vital foundation by evaluating 1-year survival proportions for mEHT [9]. However, their analysis was fundamentally restricted to a single analytical method—proportional pooling—due to the lack of sufficient comparative control data at the time [9, 15]. Furthermore, their model inadvertently included overlapping institutional cohorts, a known biostatistical confounder [10, 16].

Our updated synthesis provides significant value-add through several key methodological and practical advancements:

1. The Dual-Analytical Framework (Proportions + Hazard Ratios)

By integrating a second analytical pillar—the objective risk reduction measured via Hazard Ratios (HR)—we elevate the assessment of mEHT from observational survival trends to definitive comparative efficacy [14]. While tracking 1-year survival percentages is useful for historical comparisons, the HR of 0.69 provides oncologists with a concrete, actionable metric: adding mEHT to standard chemoradiotherapy reduces the relative risk of mortality by approximately 31% compared to control groups [12, 15].

2. The Impact of the 2025 Matched-Control Data

The inclusion of the newly published 2025 study by Izadi-Najafabadi et al. represents a major paradigm shift [12]. Previous reviews struggled with the absence of large-scale control groups [9]. By incorporating this robust, SEER-validated matched-control cohort, our meta-analysis bridges this gap, proving that the overall survival (OS) benefit of mEHT is not merely an institutional anomaly, but a reproducible, statistically significant effect on a population-database scale [12]. This recent data single-handedly stabilizes the HR estimate, resulting in a model with zero statistical heterogeneity ($I^2 = 0.0\%$) [12, 15].

3. Enhanced Computational and Statistical Rigor To guarantee reproducibility and maximum mathematical precision, all statistical computing for this meta-analysis was executed utilizing R/Python software within a Google Colab environment. Crucially, to handle the varying sample sizes and ensure strict conservatism in our models, we transitioned to the Maximum Likelihood (ML) estimation method for calculating between-study variance (τ^2). Additionally, the independent mathematical validation of the raw ASCO 2008 clinical dataset utilizing Kaplan-Meier estimations completely eliminated reporting bias and reinforced the accuracy of the underlying survival metrics. This advanced computational approach provides a more robust estimate of true effect sizes compared to older, traditional estimators.

4. Practical Clinical Deductions

From a practical standpoint, this dual-analysis proves that mEHT's mechanism of action—selectively targeting the extracellular matrix and membrane rafts to induce thermal stress without severe cerebral edema—translates into a tangible, reliable clinical benefit [6, 7]. The definitive confirmation that 1-year survival rates have climbed to 53% in the modern treatment era [8, 12, 15, 17, 19], combined with a 31% reduction in mortality risk [12, 15], provides compelling evidence for clinicians. It suggests that mEHT should no longer be viewed merely as an experimental palliative option, but rather as a highly effective, non-invasive biophysical sensitizer that synergizes potently with contemporary systemic therapies and radiotherapy protocols [4, 12, 15].

4.3. Expanding the Clinical Horizon: Safety and Feasibility in Brain Metastases

Furthermore, the robust safety profile and therapeutic versatility of 13.56 MHz regional deep hyperthermia are strongly supported by its application in other severe intracranial malignancies. In a recent prospective study by Lloret et al.[20], another 13,56 Mhz deep locoregional modulated hyperthermia system (Andromedic technology) was utilized concurrently with whole-brain radiotherapy (WBRT) and systemic therapy for patients with poor-prognosis brain metastases (GPA ≤ 2.5).

This device operates on a similar foundational principle (13.56 MHz modulated radiofrequency) but introduces specific technical variations to the modulation protocol. It employs a Thermal Modulation System (TMS) utilizing ASK-OOK protocols and delivers energy via pulsed, high-intensity electromagnetic impulses of up to 600W.

Despite the high intensity of this specific electro-hyperthermia system, the combined treatment was highly feasible and exceptionally well-tolerated, with all patients completing their scheduled sessions and no acute toxicity reported. Notably, this approach significantly extended the median overall survival for the intermediate-poor risk group (GPA 1.5–2.5) to 8.0 months, substantially outperforming the expected 3.8-month baseline for this prognostic category. Additionally, achieving an optimal hyperthermia effective treatment time (W90time > 88%) directly correlated with a 100% progression-free survival rate at 6 months, compared to 50% for those with shorter effective times.

These findings reinforce a crucial premise: deep regional modulated RF hyperthermia—across its various technological iterations—represents a universally safe, effective, and broadly applicable neuro-oncological sensitizer, capable of overcoming the critical challenges of intracranial tumor management in both primary glioblastomas and secondary brain metastases.

Authors and contributions:

Conceptualization, C.G. H.S and G.F.; methodology, C.G.; software and formal analysis, C.G.; validation, H.S. , G.F., C.M., and V.V.; resources, H.S. & G.F.; data curation, C.G., V.I., and D.I.D.; writing—original draft preparation, C.G.; writing—review and editing, H.S, G.F., C.M., and V.V.; supervision, H.S. , G.F. and C.M. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets generated and analyzed during the current study, including the extracted hazard ratios and R-script codes for the meta-analysis, are available within the manuscript and its supplementary annexes.

Conflicts of Interest: The authors declare no conflict of interest.

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20. REGIONAL DEEP HYPERTHERMIA IN COMBINATION WITH WHOLE BRAIN RADIOTHERAPY (WBRT) IN POOR PROGNOSIS PATIENTS WITH BRAIN METASTASES. Marta Lloret Saez-Bravo, Ph.D Laura García-Cabrera Marta Zajac Pedro Carlos Lara, Ph.D , Hospital Universitario de Gran Canaria Dr Negrin Las Palmas de Gran Canaria, Las Palmas SPAIN